CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020560/S012

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

sNDA #: 20-560/SE1-012 MAY 26 1998

Applicant: Merck Research Laboratories

Name of Drug: Fosamax® (alendronate sodium tablets)

Indication: Glucocorticoid-induced osteoporosis.

Documents Reviewed: Volumes 1.2 and 1.18-1.24 of NDA 120-560 dated November 26, 1997.

Medical Reviewer: This review has been discussed with Gloria Troendle, M.D., HFD-510.

1. Introduction

This review will present and discuss the results of two placebo controlled, multicenter clinical trials, Study M082 (Study 82) and Study M083 (Study 83), designed to study the safety and efficacy of Fosamax® (alendronate sodium tablets) in patients with glucocorticoid-induced osteoporosis. Because details of the design and patients population have already been presented in Dr. Troendle's review dated 3 March 1998, they will not be presented in this review. The focus of this review will be the presentation of the between treatment differences in percent change from baseline in Bone Mineral Density (BMD) for Studies 82 and 83, as well as the presentation of fracture rates in both placebo and fosamax group. In contrast to Dr. Troendle's review, the patient population analyzed will the intent to treat population regardless of whether or not they received the Protocol Defined (PD) dose of glucocorticoid, since this is more consistent with the statistical principle of "analyze as randomized".

2. Efficacy

2.1 Lumbar Spine BMD

The protocol specified primary efficacy variable was endpoint lumbar spine BMD. Figure 1 displays the estimated between treatment differences and 95% confidence intervals for lumbar spine BMD from the intent to treat analysis. For all five contrasts, the 95% confidence intervals excludes zero, indicating that each of these comparisons is statistically significant at the $\alpha = 0.05$ level.

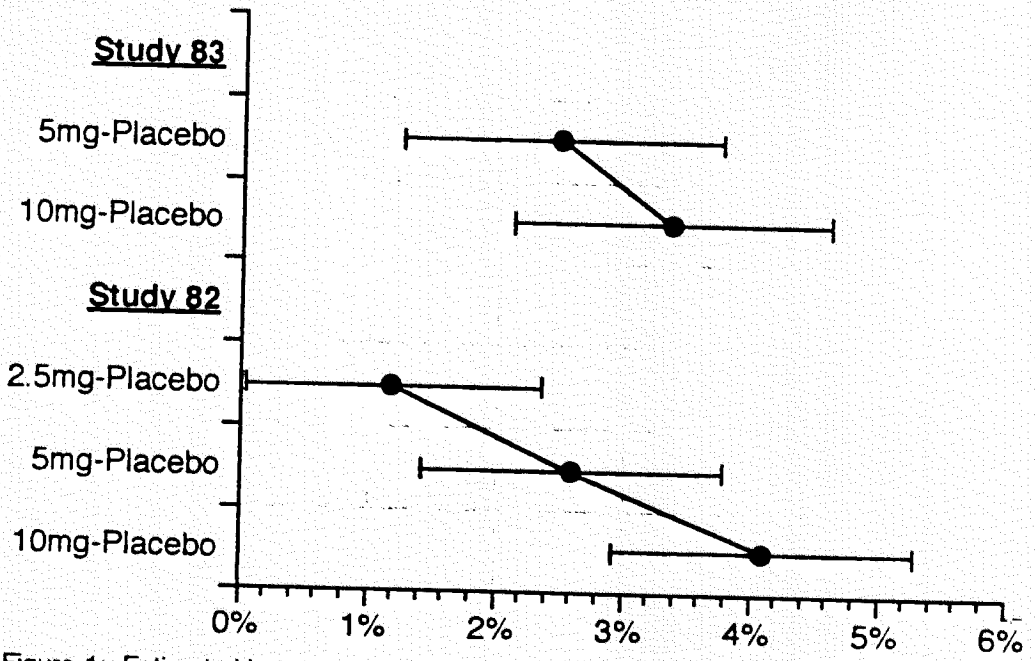

Figure 1: Estimated between treatment differences and 95% confidence intervals for lumbar spine BMD from the intent to treat analysis.

2.2 Femoral Neck BMD

A secondary efficacy variable was endpoint Femoral Neck BMD. Figure 2 displays the estimated between treatment differences and 95% confidence intervals for Femoral Neck BMD from the intent to treat analysis. With the exception of the 2.5 mg minus placebo contrast in study 82, the 95% confidence interval for the contrasts excludes zero, indicating that each of these comparisons is statistically significant at the $\alpha = 0.05$ level.

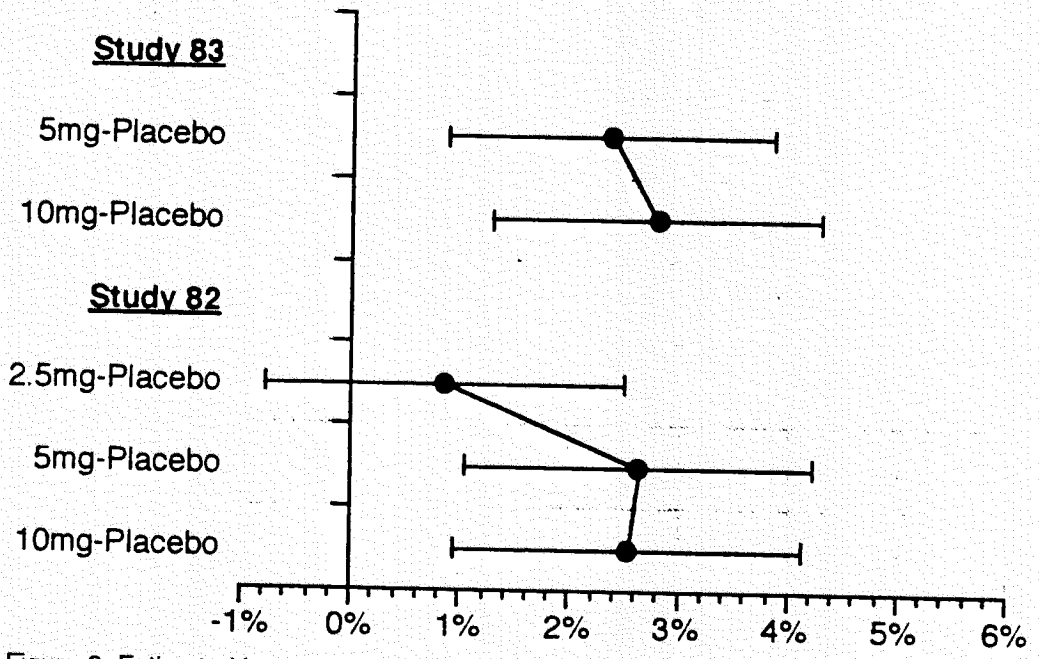

Figure 2: Estimated between treatment differences and 95% confidence intervals for femoral neck BMD from the intent to treat analysis.

2.3 Trochanter BMD

A secondary efficacy variable was endpoint Trochanter BMD. Figure 3 displays the

estimated between treatment differences and 95% confidence intervals for Trochanter BMD from the intent to treat analysis. With the exception of the 2.5 mg minus placebo contrast in study 82, and the 5 mg minus placebo contrast in study 83, the 95% confidence interval for the contrasts excludes zero, indicating that each of these comparisons is statistically significant at the $\alpha = 0.05$ level.

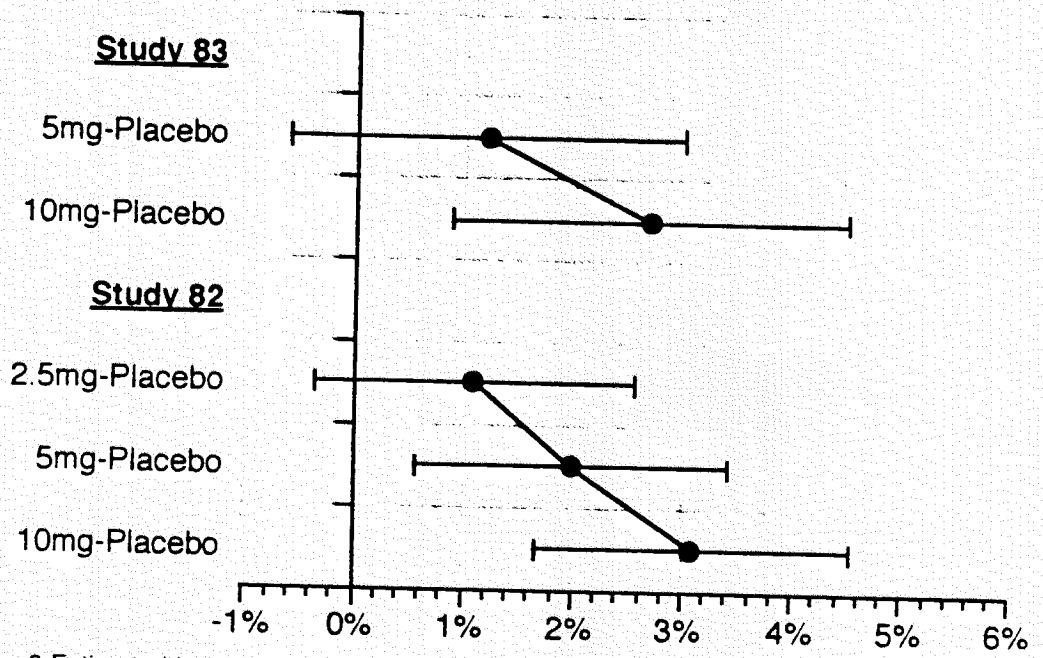

Figure 3 Estimated between treatment differences and 95% confidence intervals for trochanter spine BMD from the intent to treat analysis.

2.4 Total Hip BMD

A secondary efficacy variable was endpoint Total Hip BMD. Figure 4 displays the estimated between treatment differences and 95% confidence intervals for Total Hip BMD from the intent to treat analysis. For this variable only the 5 mg minus placebo contrast and

the 10 mg minus placebo contrast in study 82 are statistically significant at the $\alpha = 0.05$ level.

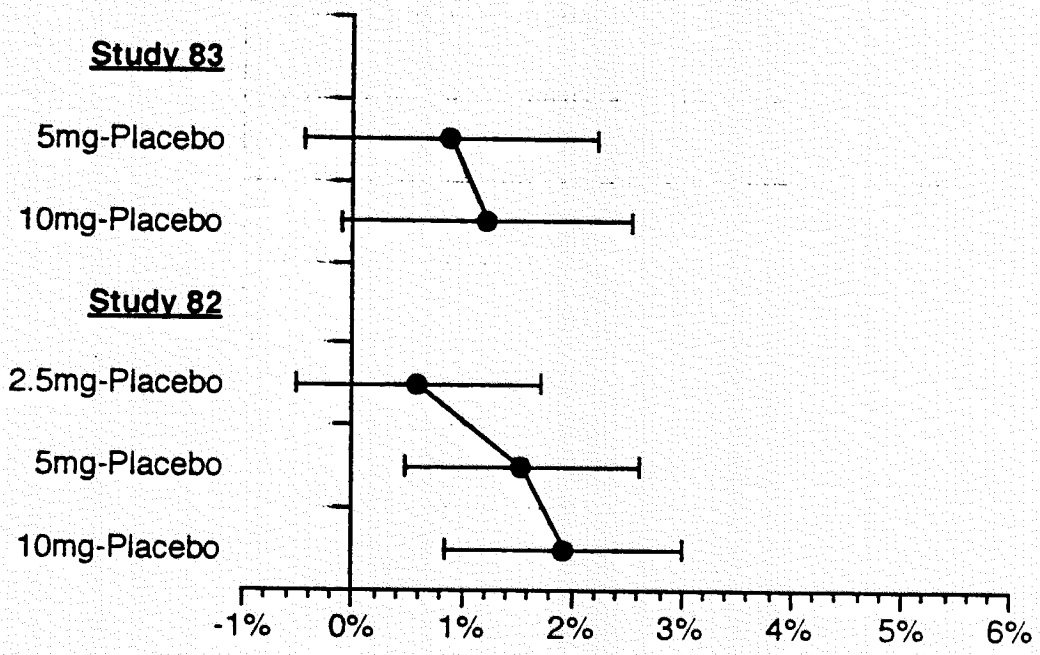

Figure 5 Estimated between treatment differences and 95% confidence intervals for total hip BMD from the intent to treat analysis.

2.5 Total Body BMD

A secondary efficacy variable was endpoint Total Body BMD. Figure 6 displays the estimated between treatment differences and 95% confidence intervals for Total Body BMD from the intent to treat analysis. For this variable only the 2.5 mg minus placebo contrast in study 82, and the 10 mg minus placebo contrast in study 83 are statistically significant at the $\alpha = 0.05$ level.

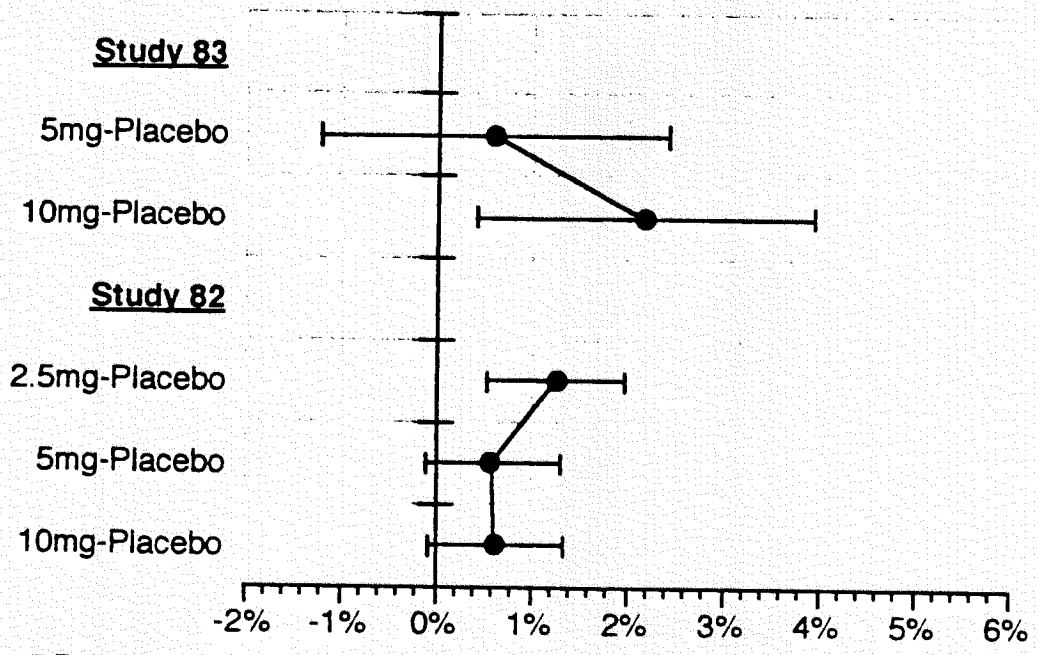

Figure 7 Estimated between treatment differences and 95% confidence intervals for total body BMD from the intent to treat analysis.

3. Fracture Rates

Figure 8 presents a dot plot of the fracture rates for the US and Multinational studies broken down by type of fractures. The open triangles represent the placebo rates, and the filled triangles represent the Fosamax rates. The most notable feature of this display is that for the US study (STudy 83) the vertebral and rib fractures are greater in the placebo group than in the fosamax group, while the fracture rates for the other types of bone are greatest in the Fosamax group. For the multinational study (Study 82), we see fewer fractures overall, and the between treatment differences for all types of bone are smaller than in the US study.

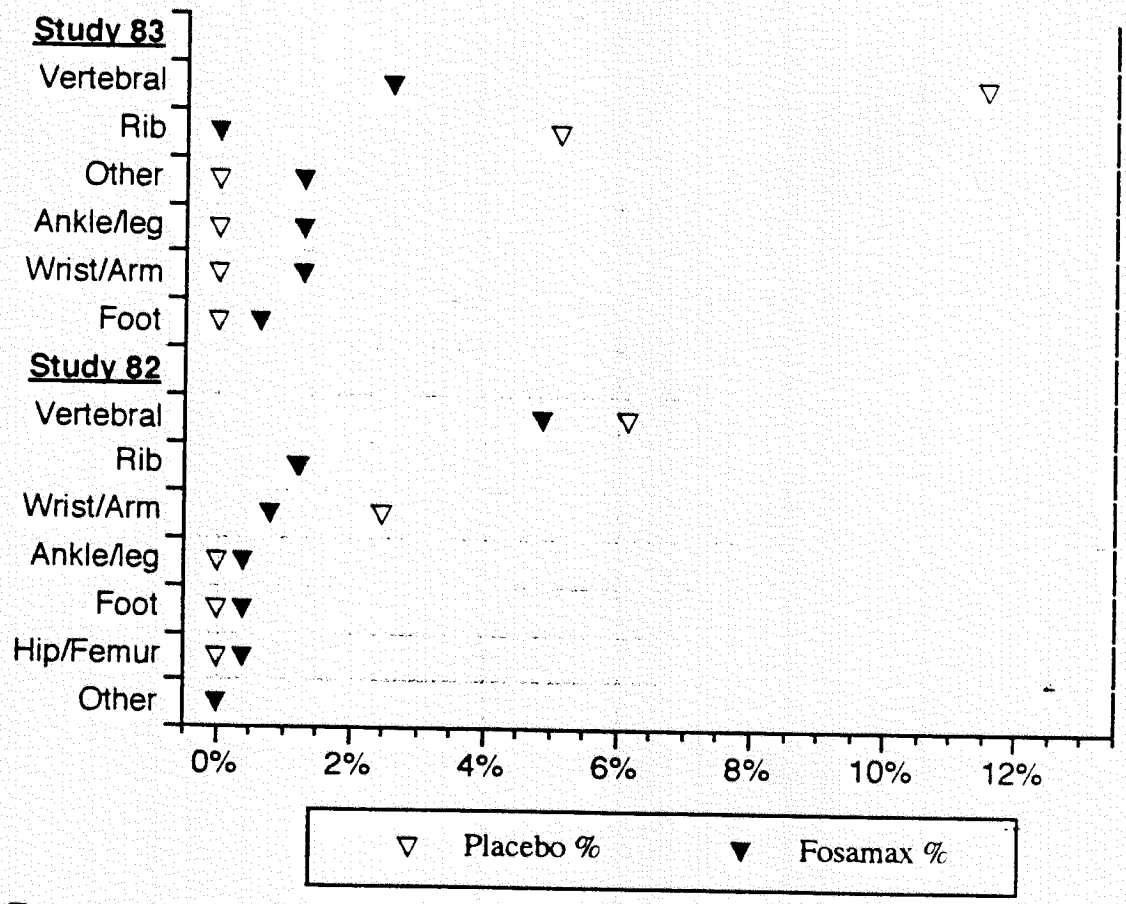

Figure 8 Estimated fracture rates classified by study and type of fracture.

The number of fractures broken down by study, treatment, and type of fracture are shown in tabular form are shown in Table 1.

Table 1: Table of number of fractures from studies 82 and 83.

Study	*Fosamax*			*Placebo*		
	Vertebral and Rib Fractures					
	# Fractures	*N*	*%*	*# Fractures*	*N*	*%*
US Study 83						
Vertebral	4	154	3%	9	78	12%
Rib	0	154	0%	4	78	5%
Total	4	154	3%	13	78	17%
Multinational Study 82						
Vertebral	12	247	5%	5	81	6%
Rib	3	247	1%	1	81	1%
Total	15	247	6%	6	81	7%
	Other Fractures					
	# Fractures	*N*	*%*	*# Fractures*	*N*	*%*
US Study 83						
Ankle/leg	2	154	1.3%	0	78	0.0%
Foot	1	154	0.6%	0	78	0.0%
Hip/Femur	0	154	0.0%	0	78	0.0%
Wrist/Arm	2	154	1.3%	0	78	0.0%
Other	2	154	1.3%	0	78	0.0%
Total	7	154	4.5%	0	78	0.0%
Multinational Study 82						
Ankle/leg	1	247	0.4%	0	81	0.0%
Foot	1	247	0.4%	0	81	0.0%
Hip/Femur	1	247	0.4%	0	81	0.0%
Wrist/Arm	2	247	0.8%	2	81	2.5%
Other	0	247	0.0%	0	81	0.0%
Total	5	247	2.0%	2	81	2.5%

Figure 9 shows confidence intervals and p-values for the Fosamax minus placebo difference in fracture rates broken down by study and type of fracture. For each difference two confidence intervals and two p-values are presented. The blue triangle represents the difference in proportions between Fosamax and placebo, the narrow blue, thick-lined a normal theory based approximate 95% z-confidence interval that will tend to be

anticonservative (have confidence less than 95%), and the wider red, thin-lined confidence interval represent an exact, unconditional confidence interval that will tend to be conservative (have confidence greater than 95%). For each of these comparisons, two p-values were calculated. One is a normal theory based approximate z-test p-value that uses a pooled estimate of the variance, and the other is the p-value from Fisher's exact test. The z-test p-value will tend to be anticonservative, while Fisher's exact test will tend to be conservative. These p-values are shown in Table 2.

Table 2: Table of p-values for between treatment differences (Fosamax minus placebo) in fracture rates from studies 82 and 83.

	Type of Fracture	
	Vertebral/Rib	*Non-Vertebral/Rib*
Study 83		
z-Test	0.0001	0.0559
Fisher's Exact Test	0.0002	0.0986
Study 82		
z-Test	0.6703	0.8100
Fisher's Exact Test	0.6116	0.6837

For the Study 83 vertebral/rib fracture rate difference, we see that Fosamax reduces vertebral/rib fractures, and all of the p-values (z p-value=.0001, Fisher's Exact p–value=.0002) and confidence intervals indicate that this difference is statistically significant. For the Study 82 vertebral/rib fracture rate difference, we see that the between treatment fracture rate differences are essentially zero, and that the p-values (z p–value=.6703, Fisher's Exact p-value=.6116) and confidence intervals are all in agreement.

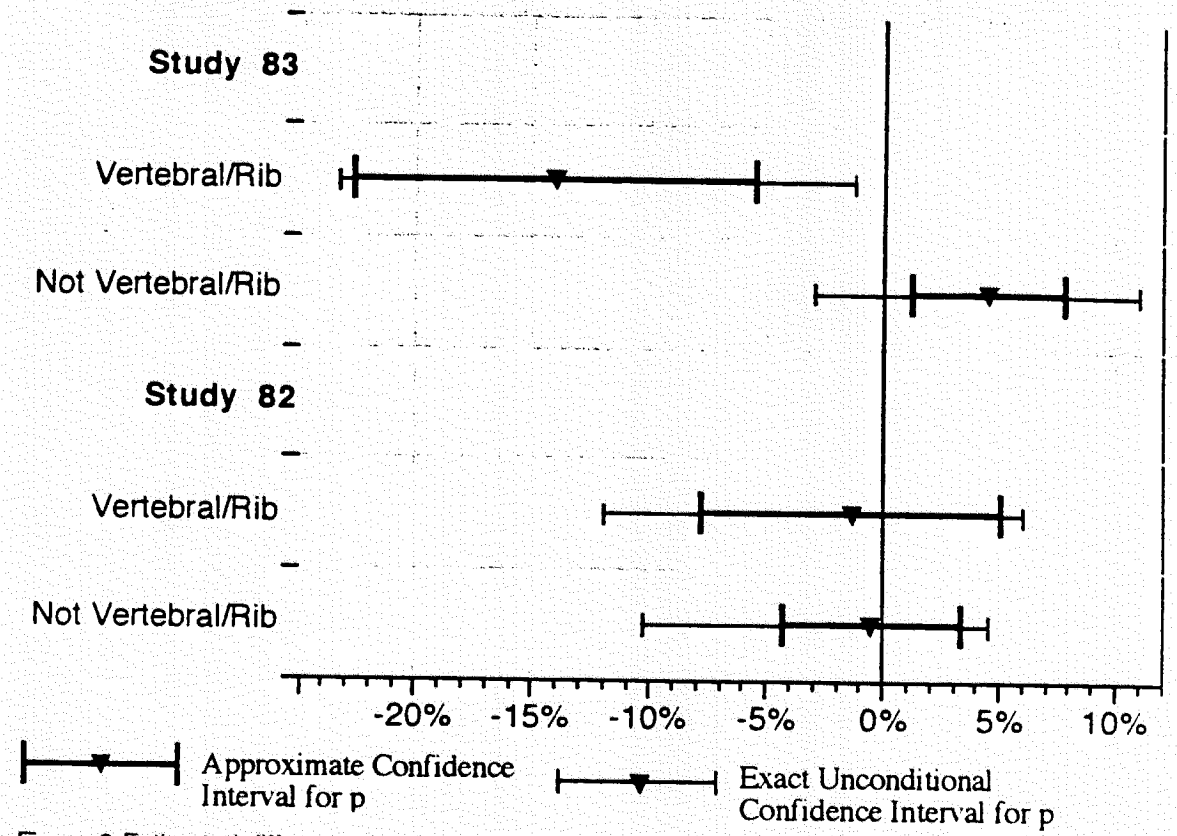

Figure 9 Estimated difference between fracture rates (Fosamax-Placebo) and 95% confidence intervals classified by study and type of fracture.

Similarly, for the Study 82 non-vertebral/rib fracture rate difference, we see that the between treatment fracture rate differences are essentially zero, and that the p-values (z p-value=.8189, Fisher's Exact p-value=.6837) and confidence intervals are all in agreement.

For the Study 83 Non-Vertebral Fracture rates the picture is less clear. The z-theory approximate p-value (0.0559) and the Fisher's exact test p-value (0.0986) are small, and suggest that Fosamax is associated with increased rates of Non-Vertebral Fractures, but do not meet the usual definition of statistical significance. In contrast, the normal theory based confidence interval indicates a statistically significant increase in Non-Vertebral Fracture rates in the Fosamax group.

4. Conclusions

Both studies 82 and 83 indicate that Fosamax produces statistically significant ($p<0.05$) improvements in lumbar spine BMD, as well as in many of the secondary BMD measurements. It is not clear what affect Fosamax has on the frequency of fractures. In Study 82, the Fosamax minus placebo difference in fracture rates for both veterbral/rib and non-vertebral fractures did not achieve statistical significance ($p>0.60$). In Study 83 the Fosamax minus placebo difference in fracture rates for veterbral/rib fractures indicated that Fosamax reduces veterbral/rib fractures, achieved statistical significance ($p<0.05$), while the Fosamax minus placebo difference in fracture rates for non-veterbral fractures suggested that Fosamax increases non-veterbral fractures, and approached statistical significance ($p<0.10$).

In summary, it is this reviewer's conclusion, based upon these two studies, that:

1) Fosamax increases lumbar spine BMD relative to placebo.
2) Fosamax either has no effect on, or reduces, the risk of veterbral/rib fractures.
3) Fosamax either has no effect on, or increases, the risk of non-veterbral fracture.

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Concur:

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APPEARS THIS WAY ON ORIGINAL